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**Serial N°:** 10/811,727

**Filed :** March 29, 2004

**Title :** New gamma crystalline form of perindopril tert-butylamine salt

**Art Unit :** 1626

**Examiner :** SHIAO

Honorable Commissioner of Patents and Trademarks

Alexandria, V.A. 22313-1450

**DECLARATION UNDER 37 CFR 1.132**

I, Gérard COQUEREL, a citizen of France, of 192, rue de l'Eglise, 76520 Boos, France, declare and say that :

I hold the degree of Doctor of University of Rouen, Faculty of Science, in 1986.

Since 1988, I have been Professor of solid state chemistry at the University of Rouen Mont-Saint-Aignan, France.

I am the author or co-author of more than 200 international publications such as patents, scientific publications, chapters of books and communications.

I am one of the co-inventors of US Patent Application Serial n° 10/811,727 filed March 29, 2004 concerning " New gamma crystalline form of perindopril tert-butylamine salt".

I am thoroughly familiar with the above-mentioned patent application and fully support the experiments contained therein which were performed either by me or under my supervision. I also fully support the conclusions derived therefrom and the arguments presented as concerns the novelty and inventive step of the crystalline form described.

Step 3D of US 4,914,214 has been reproduced with the use of rapid cooling (Experiment 1). The X-ray diffraction spectrum of the product obtained makes it possible to say that its structure does not correspond to the  $\gamma$  structure and approaches that of a hydrated beta structure.

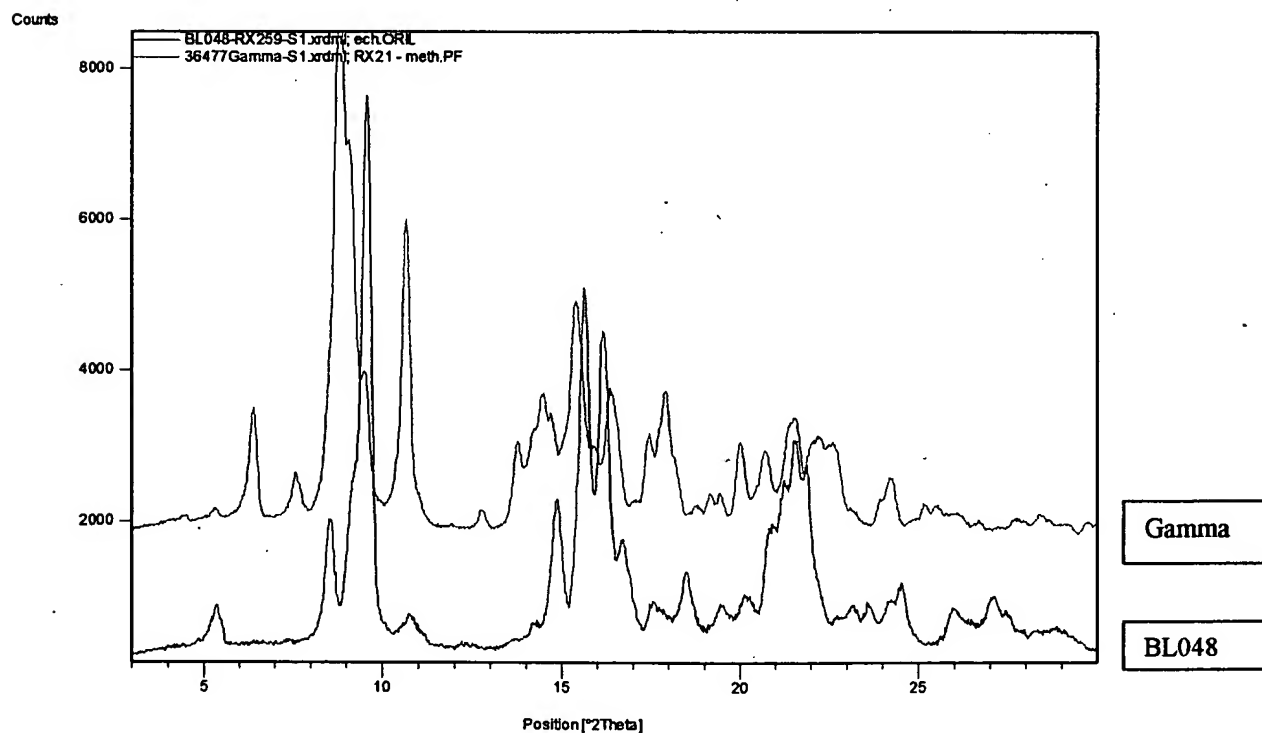
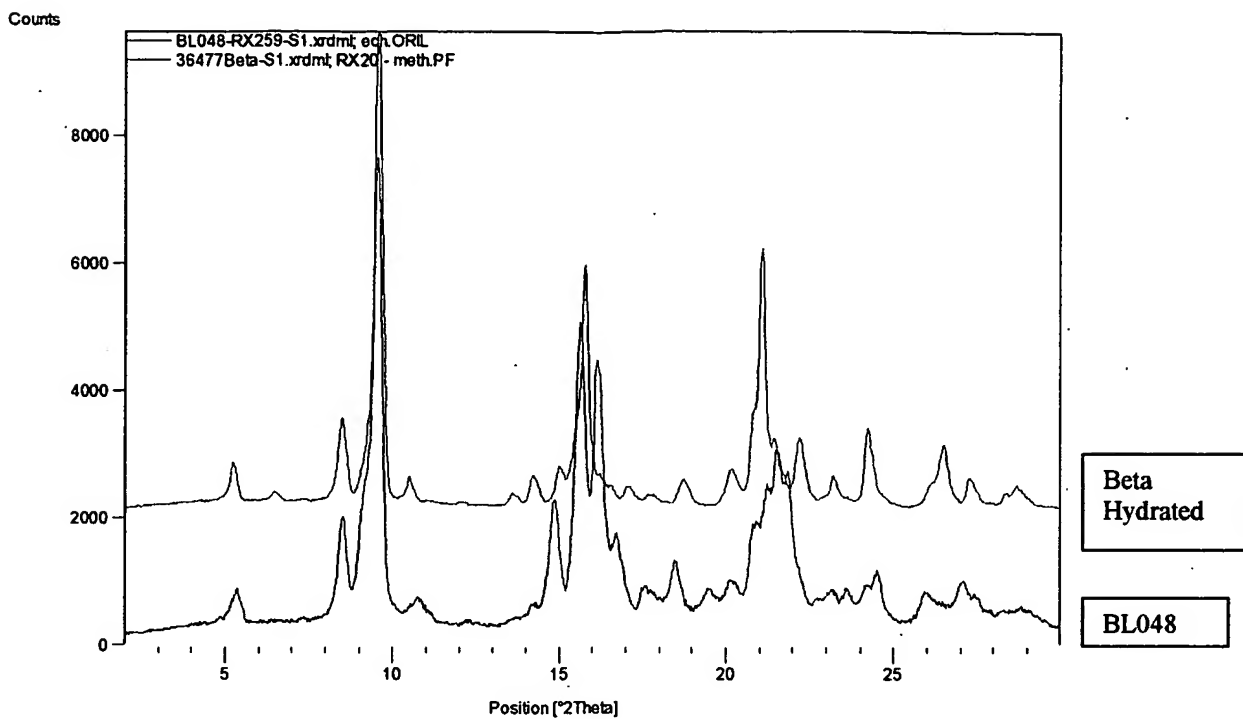
### EXPERIMENT N°1

#### REPRODUCTION OF STEP 3D OF US 4,914,214

There are introduced into a reactor 14 ml of ethyl acetate and 1 g of (2S,3aS,7aS)-1-((2S)-2-[(1S)-1-(ethoxycarbonyl)-butylamino]-propionyl)-octahydro-1H-indole-2-carboxylic acid containing 2% of impurities. To the above mixture are added 2,2 g of tert-butylamine. The mixture is then brought to reflux until complete dissolution, filtered, cooled (rapid cooling to  $-15^{\circ}\text{C}$ ), filtered and dried at  $40^{\circ}\text{C}$ , to produce 0,83 g of product.

#### RX spectrum of the form obtained in experiment n°1

No.	Pos. [ $^{\circ}2\theta$ ]	Area [cts $^{\circ}2\theta$ ]	Normalized Area (%)	d-spacing [Å]
1	5,4	49	6,85	16,396
2	8,6	308	21,72	10,301
3	9,1	291	24,65	9,683
4	9,6	1774	100,00	9,238
5	10,7	54	4,55	8,230
6	14,2	27	1,88	6,224
7	14,9	389	23,53	5,958
8	15,6	947	61,58	5,665
9	16,3	386	46,67	5,449
10	16,7	186	15,70	5,294
11	17,6	66	4,68	5,042
12	18,5	132	10,19	4,784
13	19,5	63	3,34	4,546
14	20,1	54	4,53	4,411
15	20,8	154	16,24	4,267
16	21,2	230	24,37	4,185
17	21,5	392	33,12	4,125
18	21,9	222	26,88	4,055
19	23,2	62	3,78	3,838
20	23,6	50	4,21	3,766
21	24,6	109	9,23	3,623
22	25,9	114	5,34	3,434
23	27,1	134	7,10	3,287
24	27,4	62	4,39	3,249



The X-ray diffraction spectrum of the product obtained makes it possible to say that its structure does not correspond to the gamma structure and approaches that of a hydrated beta structure.

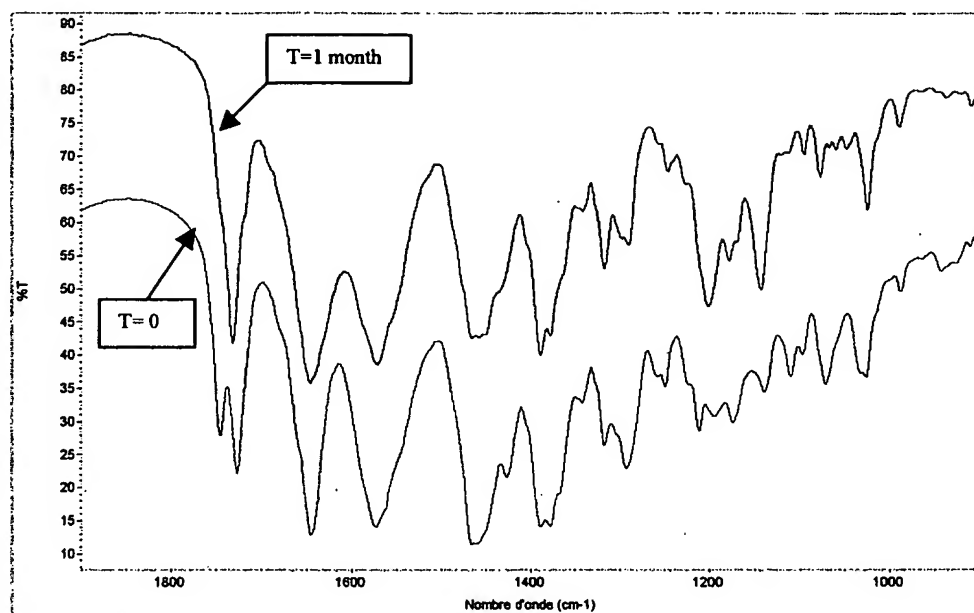
Therefore, the above experiment n°1 shows that the gamma form is not inherently disclosed in US 4,914,214.

## EXPERIMENT N°2

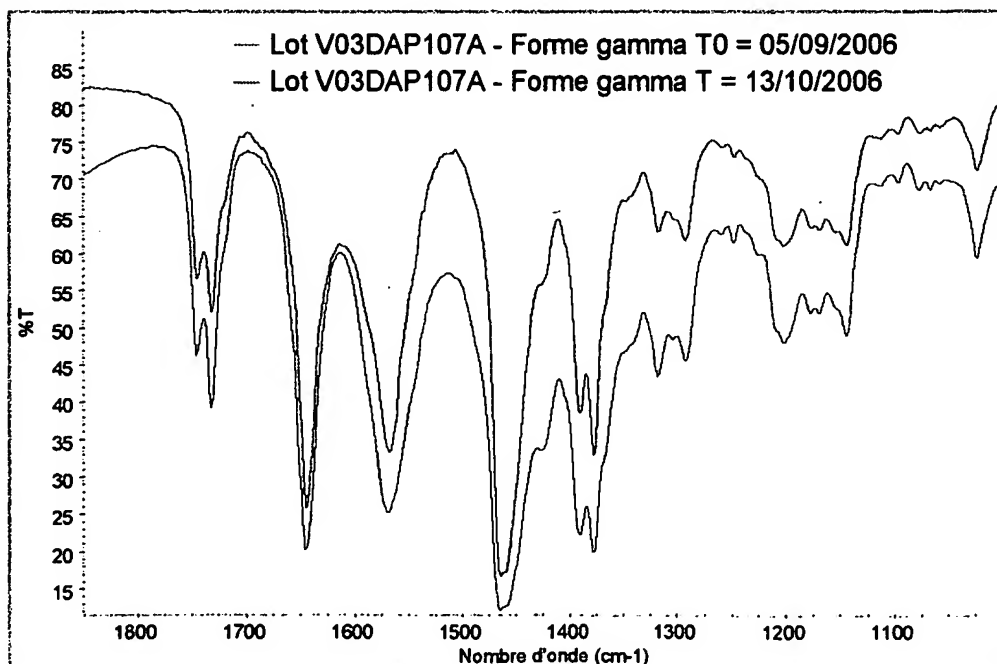
A study was made of the relative stability of the product obtained in Experiment n°1 and of the gamma form according to the invention, by studying the change over time in the IR spectra under normal storage conditions.

### Stability over time of the $\gamma$ and $\beta$ hydrated crystalline forms

**Figure 1 : Stability at T=1 month of the  $\beta$  hydrated form obtained in trial BL048 (normal storage conditions)**



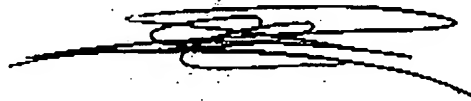
**Figure 2 : Stability at T= 37 days of the  $\gamma$  form (normal storage conditions)**



It can be seen that the gamma form according to the invention has improved stability over the form obtained by reproducing the process disclosed in Step 3D of US 4,914,214.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of the title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not



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